IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	**MDL No. 2:14-mn-02502-RMG** **This Document Relates to All Actions**

PFIZER INC.'S MOTION TO EXCLUDE EXPERT TESTIMONY AND CLAIMS THAT LIPITOR IS NOT EFFECTIVE FOR AND SHOULD NOT BE APPROVED FOR PRIMARY PREVENTION IN WOMEN AND MEMORANDUM IN SUPPORT

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page

Cases

Statutes and Rules

Other Authorities

Defendant Pfizer Inc. respectfully moves, pursuant to Federal Rules of Evidence 104(a), 702, 703, and 401, 402, and 403, to exclude expert testimony and other evidence, claims, or statements that Lipitor (1) should not be indicated for its approved use of reducing the risk of cardiovascular disease in women without clinically evident coronary heart disease but with multiple risk factors for heart disease and (2) is not effective for such use. A full explanation of the motion is provided in the supporting memorandum herein.

PRELIMINARY STATEMENT

Lipitor (atorvastatin) is a prescription medicine approved for use by both men and women to lower cholesterol and, among other approved uses, to reduce the risk of cardiovascular disease (CVD) in patients who do not have clinically evident coronary heart disease (CHD), a type of CVD that can cause heart attacks and chest pain, but who have multiple risk factors for CHD. This approved use, or "indication," is commonly referred to as "primary prevention." "Secondary prevention," by comparison, generally refers to treatment to prevent a cardiovascular event in patients who have a history of CHD. The Food and Drug Administration (FDA) first approved Lipitor in 1996, and in 2004, it approved Lipitor for primary prevention of CVD in adults. It later approved Lipitor for secondary prevention. Lipitor is one of a class of cholesterol-lowering medications known as statins.

Lipitor is one of the best-studied and most-prescribed prescription medicines in history. More than 29 million people in the United States have been prescribed Lipitor and it has more than 250 million patient-years of experience. Lipitor has been studied in more than 400 clinical trials, including many large cardiovascular outcomes trials that studied safety and efficacy in thousands of patients over multiple years. Generic atorvastatin has been available for sale in the United States since 2011, and physicians continue to widely prescribe both Lipitor and atorvastatin. The medical community views Lipitor and other statin medications as important therapies that have provided essential treatment to millions of patients, including women, who are at risk for heart attacks, strokes, and other potentially fatal manifestations of CVD.

Despite its approval for use and its demonstrated efficacy in both men and women, Plaintiffs and some of their experts seek to tell jurors that Lipitor is ***not*** effective for primary prevention in women and should not be indicated for that use. They allege that Pfizer was negligent and that it misled doctors by including this approved indication in the labeling for Lipitor and in its marketing of the medicine. And Plaintiffs want these experts to testify at trial that for a woman who has not had a heart attack or been diagnosed with CHD, there is ***no*** benefit to taking Lipitor, only risk. For example,

- John Abramson, M.D., a non-practicing physician and professional expert witness, opines that "there is no significant evidence that Lipitor provides a benefit in primary prevention women, that is, those without pre-existing heart disease," Abramson Rpt. (Ex. 1) ¶ 574;
- Barbara Roberts, M.D., a doctor who has written a book criticizing statins, opines that "Lipitor has not been shown to be beneficial in lowering the risk of cardiac events in women without established vascular disease," Roberts Rpt. (Ex. 2) at 26;
- Martin Wells, Ph.D., a statistician, opines that "Pfizer's claims of clinical proof that Lipitor reduces 'risk of heart attack … in patients with multiple risk factors for heart disease ...' is not scientifically supported for the female population," Wells Rpt. (Ex. 3) ¶ 23; and
- G. Alexander Fleming, M.D., a regulatory expert, opines that the approved primary prevention indication is "misleading with respect to efficacy in women" and that additional language should have been included in the label. Fleming Rpt. (Ex. 4) at 35.

Importantly, in offering these opinions, Plaintiffs' experts do not purport to rely on any new or allegedly undisclosed evidence or data. They concede that when FDA approved Lipitor for primary prevention in both men and women in 2004, FDA had the same data on which these experts rely for their opinions today, namely, clinical trial data from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). Plaintiffs' experts simply disagree with FDA's analysis of those data and its decision to approve Lipitor for primary prevention in women. They would like to rewrite the labeling and several would make prescribing Lipitor for primary prevention in women an "off-label" use. *See, e.g.*, Abramson Tr. (Ex. 5) at 18:17-19:14. Notably, Dr. Fleming, Plaintiffs' regulatory expert, whose testimony is the subject of a separate *Daubert* motion, testified that he knew of no relevant information withheld from FDA when FDA made

the determination that Lipitor is efficacious for primary prevention in women, and he makes no claim that the indication should be withdrawn. *See* Fleming Tr. (Ex. 6) at 224:7-226:21.

Further, several of Plaintiffs' experts, including Drs. Abramson, Roberts, and Wells, have publicly opined that Lipitor does not work for primary prevention in women for years, including, in Dr. Abramson's case, in a lawsuit filed nearly ten years ago that was dismissed before expert discovery, including, in part, on preemption grounds. *Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d 1228 (S.D. Fla. 2007). Their "no efficacy in women" hypothesis is thus not based on "hidden" or confidential Pfizer documents. Nor has it ever been accepted by the mainstream medical or scientific community, resulted in a labeling change, or been offered as expert testimony in court. This is not surprising given that it stands directly at odds with the overwhelming consensus of the world's public health authorities, medical associations, and physicians and researchers in the relevant fields, including cardiovascular health, lipidology, and epidemiology, that Lipitor provides primary prevention benefit to both men and women. In particular, Plaintiffs' experts' opinions contradict FDA's approval of Lipitor for primary prevention in women and the evidence-based cardiovascular treatment guidelines published by, among other organizations, the American Heart Association (AHA), the American College of Cardiology (ACC), and the American Diabetes Association (ADA), all of which endorse statins for men and women for primary prevention. In addition, among Plaintiffs' other experts with clinical backgrounds, several admit that they do not offer opinions that statins are ineffective for women, several testified that they prescribe statins for women and believe they work for both men and women, and several, including Drs. Gale and Singh, have published peer-reviewed literature recognizing the benefits of statins without any gender limitation.[1] *See* Singh Tr. (Ex. 9) at 36:10-38:3, 74:19-

[1] *See* Mills et al., *Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials*, 104 QJ Med. 109, 119 (2011) (Ex. 7) (co-authored by Dr. Sonal Singh). Dr. Singh and his coauthors concluded: "There are few interventions in health care that offer such favorable outcomes and so improving access to [statin] treatment and adherence to therapy should be a prime concern for physicians and public health." *Id.* at 120. *See also* Skyler et al., *Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA*

75:12, 168:15-170:25; Gale Tr. (Ex. 10) at 19:13-20:9, 125:25-126:17, 321:21-323:11; Murphy Tr. (Ex. 11) at 32:5-6, 84:19-21.

For these reasons and those set forth below, Plaintiffs' experts' opinions that Lipitor is not effective for primary prevention in women should be excluded under the Federal Rules of Evidence because the opinions are not scientifically reliable under *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and its progeny. To the extent that Plaintiffs' experts purport to apply a methodology to support their opinion that Lipitor does not work in women for primary prevention, it does not pass *Daubert*. They rely on cherry-picked, results-driven presentations of the data that unscientifically discount the replicated findings of efficacy in women in individual randomized controlled clinical trials and robust meta-analyses. They also make unsupported, conspiracy-theory like claims of bias about the authors of those studies and the treatment guidelines. Drs. Abramson, Fleming, and Wells rely on Dr. Wells's litigation-driven analysis of the ASCOT data, which Dr. Wells admits applies a non-standard statistical test, is not published and has not been peer-reviewed, and does not follow the testing directed by the ASCOT protocol and conducted by Pfizer and FDA. Plaintiffs' experts also fail to identify any plausible biological explanation for the difference they claim exists between the effect of statins in men and women. In sum, their views are not scientific and have no place in court. Their testimony would be error in any trial and could threaten public health. Plaintiffs should not be permitted to advance before a jury, in the guise of expert evidence, misinformation about the benefits of a medicine that doctors have prescribed to millions of women to reduce their risk of potentially fatal cardiovascular events.

Plaintiffs' experts' opinions should also be excluded – and Plaintiffs should be precluded from asserting any claims for liability based on a purported lack of efficacy of Lipitor for

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Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association, 53(3) J. Am. Coll. Cardiol. 298 (2009) (Ex. 8) (co-authored Dr. Edwin Gale). Dr. Gale endorsed the AHA and ADA's guidelines "[f]or primary and secondary CVD risk reduction in patients with diabetes," including those involving "lipid lowering with statins." *Id.* at 303.

primary prevention in women – because they conflict with FDA's approval of Lipitor for that use and are thus preempted by federal law. Congress vested FDA with exclusive authority to determine whether prescription medicines are effective for an intended use. *See* 21 U.S.C. § 393(b). In July 2004, FDA approved Lipitor for primary prevention in men and women with risk factors for CHD. It did so based on its informed scientific analysis of the same data on which Plaintiffs' experts base their opinion that Lipitor has not been shown to be effective for primary prevention in women. Under *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011), state-law claims that disrupt the objectives of Congress or would impose a duty that a manufacturer cannot independently satisfy while also complying with its obligations under federal law – such as Pfizer's duty to sell Lipitor consistent with its FDA-approved labeling – are preempted. This rule applies to claims that would require a label to carry information about efficacy that is different than what FDA approved when it looked at the same data. *In re Celexa and Lexapro Mkt'g & Sales Practices Litig.*, 779 F.3d 34, 40-43 (1st Cir. 2015).

Even if Plaintiffs' experts satisfied *Daubert*, and they do not, permitting Plaintiffs and their experts to proffer evidence that Lipitor is not effective for primary prevention in women would impermissibly disrupt and undermine the federal system for prescription drug approval by inviting a lay jury to second-guess FDA's considered scientific and medical judgments, which are exercised to promote the public health. This Court should thus exclude Plaintiffs' experts' opinions and any other claim that Lipitor is not effective for primary prevention in women.

I. FACTUAL OVERVIEW

A. High Cholesterol Increases the Risk of CVD, the Leading Cause of Death

It is undisputed that CVD is the leading cause of death among adults in the United States, including women.[2] CVD can cause heart attack, chest pain, heart failure, and stroke. More

[2] CDC, Heart Disease Facts, at http://www.cdc.gov/heartdisease/facts.htm (last visited July 24, 2015); Abramson Tr. (Ex. 5) at 62:23-63:12; Roberts Tr. (Ex. 12) at 158:20-22.

women die from CVD each year than from all types of cancer combined,[3] and more women die from their first heart attack than men do.[4] It is also generally accepted that having high LDL cholesterol (LDL-C or low-density lipoprotein cholesterol), often known as the "bad cholesterol," is a major risk factor for CVD. LDL cholesterol is a fatty substance, a lipid, that does not dissolve in water or blood on its own. When there is too much LDL in the blood, it can build up in the walls of the arteries and, over time, create a plaque that impedes blood flow, a condition known as atherosclerosis. CHD involves plaque that has developed in the walls of the arteries around the heart. In addition to disrupting blood flow, the plaque can rupture and create a blood clot that leads to a heart attack or stroke. All but one of Plaintiffs' experts with medical degrees agree that elevated LDL cholesterol is a risk factor for CVD in both men and women. *See, e.g.*, Singh Tr. (Ex. 9) at 170:12-171:10, 171:23-173:6; Gale Tr. (Ex. 10) at 317:14-318:22; Abramson Tr. (Ex. 5) at 64:16-65:7; Quon Tr. (Ex. 13) at 71:8-20, 329:21-330:7; Fleming Rpt. (Ex. 4) at 7-8; *see also* Wells Tr. (Ex. 14) at 60:12-17. Dr. Roberts alone opines that high LDL is ***not*** a risk factor for CVD in women. Roberts Tr. (Ex. 12) at 25:4-7.

Based on decades of research and clinical experience, reducing LDL cholesterol has become an important and generally-accepted focus of efforts to prevent and treat CVD in both men and women. Those efforts also include preventing and treating other risk factors that contribute to the development of CVD, such as high blood pressure and obesity. Since the 1980s, expert panels and medical organizations have developed and regularly updated guidelines for treating high cholesterol in order to reduce the risk of CHD and CVD. The most recent were published by the ACC and AHA in 2013.[5]

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[3] Kochanek et al., *Deaths: Final Data for 2009*, National Vital Statistics Report (Dec. 2011), *available at* http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_03.pdf.

[4] Mozaffarian et al., *Heart Disease and Stroke Statistics—2015 Update – A Report From the American Heart Association*, 131 Circulation e29, e257-58 (2015) (Ex. 15); Abramson Tr. (Ex. 5) at 63:13-15; Roberts Tr. (Ex. 12) at 159:10-12.

[5] *See* National Heart, Lung, and Blood Institute, National Cholesterol Education Program (NCEP), *High Blood Cholesterol in Adults: Report of the Expert Panel on Detection, Evaluation, and Treatment*, NIH Pub. 88-2925 (1988) (Ex. 16); NCEP, *Second report of the expert panel on*

The guidelines include recommendations about whether and when a physician should consider adding drug therapy to dietary changes to treat elevated cholesterol, and for more than two decades, the primary recommended drug therapy has been treatment with statins. In 1985, the Nobel Prize in Medicine was awarded for the discovery of the underlying mechanisms of cholesterol metabolism and the ability to reduce cholesterol through treatment with a statin. Two years later, FDA approved the first statin, Mevacor (lovastatin). Since then, statins have been credited with revolutionizing the treatment of high LDL cholesterol, preventing heart attacks and strokes, and saving lives. *See, e.g.*, Hennekens Rpt. (Ex. 22) at 12-13; Fonseca Rpt. (Ex. 23) at 14-17. Studies have shown that the prevalence of CVD has decreased since the introduction of statin therapy, with statins identified as one of the most significant factors contributing to this trend. *See* Sacks Rpt. (Ex. 24) at 69-70. Public health organizations and experts in preventive cardiology continue to advocate for increased awareness about CVD in women and about treatment options, including the use of statins for primary prevention in women.[6]

B. Lipitor is Approved for Primary Prevention of CVD in Men and Women

Atorvastatin, the Lipitor compound, was developed in the 1980s and early 1990s by Warner-Lambert's Parke-Davis division.[7] In 1996, FDA, which previously approved four other statin medicines, approved Lipitor for use as an adjunct to diet to reduce elevated cholesterol. Atorvastatin soon after became and has remained one of the most widely-prescribed medicines in

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detection, evaluation, and treatment of high blood cholesterol in adults, NIH Pub. No 93-3095 (1994) (Ex. 17); NCEP, *Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III)*, NIH Pub. No. 02-5215 (2002) (Ex. 18); Grundy et al., NCEP, *Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines*, 110 Circulation 227 (2004) (Ex. 19); Stone et al., *2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults*, 129 Circulation 1 (2014) (Ex. 20); *see also* Rarick Rpt. (Ex. 21) at 35-38.

[6] *See, e.g.*, National Heart, Lung, and Blood Institute, How Does Heart Disease Affect Women?, at http://www.nhlbi.nih.gov/health/health-topics/topics/hdw (Apr. 21, 2014); Michos, *The prevention of cardiovascular disease among women*, in *ASPC Manual of Preventive Cardiology*, 174, 178-80 (Wong et al. eds., 2015) (Ex. 25).

[7] Pfizer acquired Warner-Lambert in 2000.

the United States. FDA approved new indications for Lipitor in: 1998, for patients with elevated triglycerides, another blood lipid that can increase the risk of CVD; 1999, to increase HDL cholesterol, the "good cholesterol"; 2002, for certain pediatric use; 2004, for primary prevention of CVD; 2005, to reduce the risk of heart attack and stroke in patients with type 2 diabetes but without CHD and to reduce the risk of stroke as part of the primary prevention indication; and 2007, for secondary prevention, namely, to reduce the risk of non-fatal heart attack, stroke, revascularization, hospitalization for heart failure, and angina, in patients with CHD.[8]

For primary prevention, the "Indications and Usage" section of the Lipitor labeling states:

> In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to:
>
> - Reduce the risk of myocardial infarction [heart attack]
> - Reduce the risk of stroke
> - Reduce the risk for revascularization procedures and angina.[9]

The primary prevention indication does not include any gender-based statement or restriction.

Plaintiffs and several of their experts contend that Lipitor is not effective for and should not have been approved for primary prevention in women. *See, e.g.*, Master Compl. ¶¶ 1, 18, 163. Their claims implicate the federal regulatory system for the approval of prescription medicines. Before marketing a prescription medicine in interstate commerce, a manufacturer must obtain approval for the drug from FDA. *See* 21 U.S.C. § 355(a). The FDA drug approval process is "onerous and lengthy." *Mut. Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466, 2471 (2013). For a new brand-name medicine such as Lipitor, the manufacturer must submit a new drug application (NDA), including, among other things, "full reports" of all clinical investigations, relevant nonclinical studies, and "any other data or information relevant to an

[8] *See* FDA, Lipitor Approval History, at http://tinyurl.com/688cm (last visited July 24, 2015) (search "Lipitor," click "Approval History").

[9] March 2015 Lipitor Label (Ex. 26).

evaluation of the safety and effectiveness" of the drug. 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d)(5)(iv). The application must include the proposed label, 21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.50(c)(2)(i), and an explanation why the medicine's "benefits exceed the risks under the conditions stated in the labeling." 21 C.F.R. § 314.50(d)(5)(viii); *id*. § 314.50(c)(2)(ix). A similar submission, known as a supplemental NDA (SNDA) is required when a manufacturer seeks approval of a new indication for an approved medicine. "All procedures and actions that apply to [an NDA] under § 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change." 21 C.F.R. § 314.71(b); *see also* Rarick Rpt. (Ex. 21) at 12-15.

A new indication may be approved only if the manufacturer submits "substantial evidence that the drug will have the effect it … is represented to have." 21 U.S.C. § 355(d); *see also* 21 C.F.R. § 314.126. A proposed label undergoes rigorous review as well. FDA must find that a proposed label is accurate and not "false and misleading in any particular." 21 U.S.C. § 355(d). A label must discuss the clinical studies that "support effectiveness for the labeled indication(s)." 21 C.F.R. § 201.57(c)(15). FDA's "strict" standards, *Weinberger v. Hynson*, 412 U.S. 609, 619 (1973), are among "'the world's most demanding.'" Catherine M. Sharkey, *Prod. Liab. Preemption: An Institutional Approach*, 76 Geo. Wash. L. Rev. 449, 503 n.258 (2008) (citation omitted); *see also Grundberg v. Upjohn Co.*, 813 P.2d 89, 96 (Utah 1991).

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) was a CVD outcomes trial that compared patients taking Lipitor 10 mg against patients taking placebo. The trial, which began recruiting patients in 1998, was designed to evaluate different treatment strategies to prevent CVD in patients with high blood pressure (hypertension) and at least three other risk factors for CVD. More than eighty-one percent of the approximately 19,000 ASCOT participants were male, and being male was one of the qualifying risk factors for CVD.[10] The study was not designed, or "powered," to evaluate efficacy specifically in women,

[10] Sever et al., *Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower than-average cholesterol concentrations, in the*

but rather, across the total study population. [redacted][11] [redacted][12]

In July 2004, FDA approved Lipitor for primary prevention based on the ASCOT results.[13] [redacted] The subgroup analysis did not demonstrate statistically significant reduced risk of the primary outcome among women, but the data also did not show "heterogeneity," or a statistically significant difference in treatment effect based on gender.[14] [redacted]

anglo-scandinavian cardiac outcomes trial—lipid lowering arm (ASCOT-LLA): A multicentre randomised controlled trial, 361 Lancet 1149, 1150-51 (2003) (Ex. 27).

[11] [redacted]

[12] [redacted]

[13] *See* July 30, 2004 letter from FDA to Pfizer (Ex. 30).

[14] *See* Sever (2003) (Ex. 27) at 1153.

[redacted][15] There were a total of only 36 primary endpoint events among women across the placebo and Lipitor groups, with slightly more events in the women in the atorvastatin group. [redacted][16]

FDA determined that based on the small total number of events among women during the trial, the results in women alone were inconclusive, and it included this information in the description of the ASCOT results in the label that it approved in July 2004. The label stated:

> LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs 40 events in the LIPITOR group) or nonfatal MI (108 events in the placebo group vs 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. ***Due to the small number of events, results for women were inconclusive***.

July 2004 Lipitor Label (Ex. 32) (emphasis added). Thus, FDA specifically considered the limitations in the data relating to women in determining the scope and nature of a new indication based on ASCOT. It approved the primary prevention indication without any gender-based restriction, and it also directed Pfizer to tell doctors about the inconclusive nature of the results for women in the separate section of the label describing ASCOT. As noted, since 2004, FDA has approved the Lipitor label on multiple other occasions in connection with new uses and information. It has never limited the primary prevention indication to men or otherwise reconsidered or modified its approval for primary prevention based on ASCOT.

C. The Medical Community Agrees Lipitor Is Effective for Women

The evidence that Lipitor works in women to reduce the risk of CVD has continued to build since 2004. It is well recognized both that women have been underrepresented in statin

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[15] [redacted]

[16] [redacted] Sever (2003) (Ex. 27) at 1153.

clinical trials and that women generally experience cardiovascular events later in life than men, resulting in fewer cardiovascular events captured for women during the major statin trials, many of which were stopped early due to benefit.[17] *See, e.g.*, Roberts Tr. (Ex. 12) at 29:21-30:4; Abramson Tr. (Ex. 5) at 53:8-54:2; Jewell Tr. (Ex. 33) at 328:3-11; Singh Tr. (Ex. 9) at 174:5-175:20. With increasing study, however, there is now a wealth of clinical trial data and robust meta-analyses[18] demonstrating that statins, including Lipitor, are effective in both men and women, and in patients with and without diabetes, for reducing the risk of CVD, including heart attack, stroke, and cardiovascular death. *See, e.g.*, Hennekens Rpt. (Ex. 22) at 6-8, 56-68; Elasy Rpt. (Ex. 34) at 2-3, 15-17; Fonseca Rpt. (Ex. 23) at 17-19; Miller Rpt. (Ex. 35) at 19-23; Sacks Rpt. (Ex. 24) at 40-44; Sacks Rebuttal Rpt. (Ex. 36) at 6-14; Waikar Rpt. (Ex. 37) at 14-16; Wei Rpt. (Ex. 38) at 16-17. The evidence includes:

- **CARDS (2004)** (randomized trial assessing the efficacy of atorvastatin 10 mg for primary prevention in patients with type 2 diabetes without high LDL): The trial ended early because of demonstrated efficacy. Atorvastatin was associated with significant reductions in acute CHD, coronary revascularization, stroke, and death for both men and women with diabetes. Prespecified heterogeneity tests showed no difference by gender.[19]

- **JUPITER (2008)** (randomized trial assessing the efficacy of rosuvastatin in individuals without elevated LDL but with elevated C-reactive protein, a marker of cardiovascular

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[17] *See, e.g.*, NIH, *Cholesterol Guidelines: The Strength of the Science Base and the Integrity of the Development Process: Statement from Barbara Alving, M.D., Acting Director of the National Heart, Lung, and Blood Institute* (September 24, 2004), *available at* http://www.nih.gov/news/pr/sep2004/nhlbi-24.htm (Ex. 39).

[18] A meta-analysis "[a]ttempts to combine information from all studies on a certain topic. For example, in the epidemiologic context, a meta-analysis may attempt to provide a summary odds ratio and confidence interval for the effect of a certain exposure on a certain disease." *Reference Manual on Scientific Evidence* 289 (3d ed. 2011).

[19] Colhoun et al., *Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): Multicentre randomised placebo-controlled trial*, 364 Lancet 685, 691 (2004) (Ex. 40); *see also* Newman et al., *The safety and tolerability of atorvastatin 10 mg in the collaborative atorvastatin diabetes study (CARDS)*, 5 Diab. Vasc. Dis Res. 177 (2008) (Ex. 41).

risk, including women): The trial ended early because of demonstrated efficacy. Women and men experienced similar significant reductions in CVD events (46% and 42%).[20]

- **Mora (2010)** (meta-analysis of data in over 13,000 women from statin primary prevention trials): The authors found that among women, "statin allocation yielded a significant [relative risk] reduction in CVD by one-third, similar to prior results seen in men and in secondary prevention in women."[21]

- **Kostis (2012)** (meta-analysis of data from 18 randomized statin clinical trials with gender-specific outcomes): The authors concluded that "[s]tatin therapy is associated with significant decreases in cardiovascular events and in all-cause mortality in women and men. Statin therapy should be used in appropriate patients without regard to sex."[22]

- **Cochrane Collaborative (2013)** (analysis of data from 18 randomized statin clinical trials with more than 56,000 participants, of whom 40% were women): This analysis found statins effective for primary prevention in patients with risk factors for CHD irrespective of gender: "Men and women, old and young, and people with and without CVD all appear to benefit."[23]

- **Cholesterol Treatment Trialists (CTT) Collaboration (2015)** (meta-analysis of data from 27 statin trials with more than 174,000 participants, including 46,000 women): The authors found that while women generally had a lower baseline cardiovascular risk than men, "[i]n men and women at an equivalent risk of cardiovascular disease, statin therapy is of similar effectiveness for the prevention of major vascular events" and that the "[b]enefits [of statins] greatly exceed known hazards, even among individuals at low absolute cardiovascular risk."[24]

- **Hsue (2015)** (analysis of the effect of Lipitor on lipid lowering, cardiovascular events, and adverse events in women compared with men in six trials): The authors found the lower the LDL cholesterol level achieved, the lower the rate of major cardiovascular events for both men and women. The authors concluded, "The results of this study show

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[20] Ridker et al., *Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein*, 359 N. Engl. J. Med. 2195 (2008) (Ex. 42).

[21] Mora et al., *Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: Results from the justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials*, 121 Circulation 1069 (2010) (Ex. 43).

[22] Kostis et al., *Meta-analysis of statin effects in women versus men*, 59 J. Am. Coll. Cardiol. 572 (2012) (Ex. 44).

[23] Taylor et al., *Statins for the primary prevention of cardiovascular disease*, Cochrane Database Syst. Rev. (2013) (Ex. 45).

[24] Cholesterol Treatment Trialists Collaboration, *Efficacy and safety of LDL-lowering therapy among men and women: Meta-analysis of individual data from 174 000 participants in 27 randomised trials*, 385 Lancet 1397 (2015) (Ex. 46).

that the effects of atorvastatin 10 and 80 mg in 6 large randomized trials did not differ markedly overall in women compared with men."[25]

Based on this extensive evidence and analyses, there is no serious scientific dispute that statins are an appropriate treatment option for women with risk factors for CHD. That such benefit is generally accepted is demonstrated by the treatment recommendations of the leading national cardiovascular medical associations, which clinicians consider the standard of care. Each endorses statins for primary and secondary prevention, without regard to gender:

- **AHA** and **ACC:** "In individuals 40 to 75 years of age with LDL–C 70 to 189 mg/dL who are without clinical ASCVD [atherosclerotic CVD] or diabetes, initiation of statin therapy based on estimated 10-year ASCVD risk is recommended, ***regardless of sex***, race or ethnicity (Section 4.7). Point estimates of statin-associated reductions in the relative risk of ASCVD in primary prevention are similar for both women and men."[26]

- **ADA:** "In all patients with diabetes aged > 40 years, and if clinically indicated, moderate intensity statin treatment should be considered, in addition to lifestyle therapy."[27]

- **National Lipid Association:** "A large body of [randomized controlled trial] evidence demonstrates that statins are safe and generally well tolerated by most patients and that they decrease risk for [atherosclerotic CVD] events in both primary and secondary prevention in amounts proportional to their atherogenic cholesterol lowering. For these reasons, they are considered to be first-line drug treatment in both primary and secondary prevention of [atherosclerotic CVD]."[28]

D. Plaintiffs' Experts Claim Lipitor Does Not Reduce CVD Risk in Women

Several of Plaintiffs' experts proffer opinions that conflict directly with FDA's approval of Lipitor for women for primary prevention and with the findings of the scores of scientists who have authored the studies, meta-analyses, and guidelines cited above. They include:

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[25] Hsue et al., *Impact of female sex on lipid lowering, clinical outcomes, and adverse effects in atorvastatin trials*, 115 Am. J. Cardiol. 447 (2015) (Ex. 47).

[26] Stone et al. (2014) (Ex. 20) at 31 (emphasis added).

[27] American Diabetes Association, *Standards of medical care in diabetes—2015*, 38 Diabetes Care 1, at S53 (2015) (Ex. 48).

[28] Jacobson et al., *National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1—Full Report*, 9 J. Clinical Lipidology 129, 136 (2015) (Ex. 49).

1. Dr. John Abramson

Dr. Abramson opines:

- "Relevant guidelines for the primary prevention of cardiovascular disease did not, and do not, contain evidence that Lipitor reduces the incidence of [cardiovascular disease] in women without pre-existing heart disease," Abramson Rpt. (Ex. 1) ¶ 21;
- "Lipitor prescriptions for women for primary prevention should be an off-label use," Abramson Tr. (Ex. 5) at 19:8-14; and
- No doctor in America has "accurate information about Lipitor." *Id.* at 68:17-19.

Dr. Abramson agrees that CVD risk in women "is about ten to fifteen years behind men's" because of a protective effect before menopause. *Id.* at 53:8-54:2. But he cannot identify any biological difference between men and women with equivalent CVD risk to support his opinion that Lipitor works in men but not women for primary prevention. *Id.* at 56:22-57:14.

For his lack-of-efficacy opinion, Dr. Abramson relies on Dr. Wells's *post hoc* statistical analysis of the ASCOT data. *See id.* at 20:17-21:9, 30:14-17. Yet he concedes that he formed the same opinion in 2005 in other litigation, and did so based on a 2005 CTT meta-analysis. *See id.* at 97:13-20, 99:16-100:12; 604:23-605:21. He describes the CTT group's statin analyses as the "best [evidence on statin efficacy] that somebody who's not in litigation can get." *Id.* at 98:22-99:8; 606:15-17. As noted above, the CTT's 2015 meta-analysis confirms that statins have similar efficacy in men and women. Dr. Abramson takes issue with the authors' decision to include certain data in that analysis, but he has never contacted the authors or the Lancet to voice his concerns. *Id.* at 610:21-611:24. He also confirmed that he bases his criticism of the CTT analysis on publicly available information, not confidential litigation documents. *Id.* at 612:6-22; *see also id.* at 305:12-18, 306:9-23. He has not independently analyzed Lipitor clinical trial data or tested his theory that Lipitor does not work for primary prevention in women.

Further, Dr. Abramson testified that he agrees:

- with the approval of Lipitor for secondary prevention in women, *id.* at 42:23-25, 60:24-61:1;
- that Lipitor reduces LDL levels in both men and women, *id.* at 66:1-5;

- that it would be within the standard of care to prescribe Lipitor to a woman with an LDL over 190 mg/dL even if she did not have CHD, *id.* at 50:1-7;
- that Lipitor may appropriately be prescribed for a diabetic patient regardless of whether the patient has clinically evident CHD, *id.* at 242:18-23; and
- that "[t]here may be" women who would benefit from Lipitor for primary prevention, but he is "not sure how to identify them," *id.* at 45:15-18.

He also admits that he has not been willing to share or advance his no-efficacy-in-women opinions in non-litigation work He testified, for example, that while he was working as a consultant to Wells Fargo from 2005 to 2012 and advising the company and its clients on how to "[r]educe unnecessary spending on pharmaceutical products," he never recommended that any customer limit its reimbursement for Lipitor for primary prevention and "never told a client that [Lipitor] doesn't work for primary prevention" even though he "believed that the evidence did not support the efficacy for women in primary prevention." *Id.* at 290:10-19, 292:21-294:18, 295:12-20, 296:9-297:7, 298:17-299:8.[29] He views "[t]he boundaries of what [he] can say or feel comfortable doing in litigation [as] different," and apparently broader, "than what [he] felt [his] boundaries were as a Wells Fargo employee" and are in his academic speaking. *Id.* at 299:9-16, 299:22-25. He testified: "It's because … I think in this [litigation] forum we can debate the facts, debate what the science shows, and that that's what this forum is about." *Id.* at 299:17-21.

2. Dr. Barbara Roberts

Dr. Roberts is a physician and professor of medicine at Brown University. She wrote *The Truth About Statins: Risks and Alternatives to Cholesterol-Lowering Drugs* (Pocket Books 2012) (Ex. 50), a book that asserts that statins have only minor relative benefits and are most effective in men with CVD. She promotes a Mediterranean diet as an alternative to statins for lowering LDL, and she contends that the medical profession, FDA, and pharmaceutical companies are an "unholy, very lucrative alliance." Roberts, *The Truth About Statins*, at 142.

[29] Dr. Abramson did, however, recommend that Wells Fargo endorse incentives for insureds to obtain higher-dose Lipitor pills and split them in half (to get the prescribed dose) to save costs, a practice FDA advises against. *Id.* at 294:6- 295:25.

She attacks the cholesterol treatment guidelines and other AHA clinical guidelines, describing them as "tainted" by "Big Pharma paymasters." *Id.* at 168-73. She writes that it would be "naïve" and "gullible" to think that although pharmaceutical companies "are for-profit entities, they 'also strive to help patients live longer and healthier lives.'" *Id.* at 171 (citation omitted). Here, she opines that:

- High LDL cholesterol is not a risk factor for CVD in women, *see, e.g.*, Roberts Tr. (Ex. 12) at 131:19-25, 166:10-16; and
- Lipitor is not effective in women for primary prevention or for female patients with diabetes and has limited efficacy for secondary prevention, *see id.* at 150:14-24, 154:15-155:1, 155:23-156:8, 167:17-19, 174:19-175:9.

Dr. Roberts disagrees with the AHA and ACC's 2013 cholesterol-treatment guidelines. *See id.* at 49:12-21, 133:6-10, 145:12-16, 148:13-23, 150:14-151:8, 155:23-156:8. Although she has not read and is "not conversant with" the ADA's treatment guidelines, *id.* at 175:10-16, 233:6-11, she disagrees with those guidelines' recommendations as to statin use in diabetic patients for primary prevention. *Id.* at 257:1-259:15. She similarly disagrees with the authors of the CTT (2015), Cochrane (2013), and Kostis (2012) meta-analyses with respect to their findings that both men and women benefit from statins for primary prevention. *Id.* at 209:23-211:11, 215:15-216:2, 216:7-22. [redacted]

At the same time, Dr. Roberts admits that she continues to prescribe statins to certain patients, Roberts Tr. (Ex. 12) at 35:13-21, 38:22-39:1, that statins "unquestionably … reduce LDL cholesterol," and that her female patients have significant LDL reduction with statins. *Id.* at 162:1-21. Dr. Roberts agrees that "Lipitor is equally effective for lowering LDL cholesterol in all groups." *Id.* at 101:10-15. She could not identify a biological explanation for why statin therapy "would be beneficial in preventing a second heart attack" (secondary prevention) "but

not a first heart attack" (primary prevention). *Id.* at 166:21-167:3. Notwithstanding these concessions, she testified that: "For primary prevention in women, I tell [patients] that there is zero evidence that taking a statin will lower their risk of heart attack or dying of heart disease or having a stroke." *Id.* at 174:19-175:9. She could not say whether hers was a minority view. *Id.* at 132:10-15.

3. Dr. Martin Wells

Dr. Wells is a professor of statistics and epidemiology at Cornell University and Medical School. He is not a physician and has no clinical expertise. Wells Tr. (Ex. 14) at 36:5-23. He seeks to testify that "[t]here is no statistically significant evidence to support the claim that statins provide primary cardioprotection for women." Wells Rpt. (Ex. 3) ¶ 4. [redacted] an outdated meta-analysis of clinical trial data relating almost exclusively to pravastatin, not Lipitor, that was included in a legal article he published with a law professor in 2008 in a legal journal of which he was the editor, *see id.* ¶¶ 16-23, Wells Tr. (Ex. 14) at 76:1-77:24, 190:1-21, 196:11-15; and his unpublished critique of recent meta-analyses that found primary prevention efficacy in women, including the CTT's 2015 meta-analysis that was based on patient-level data from 27 trials, an analysis that Dr. Wells has not done. *See* Wells Rpt. (Ex. 3) ¶¶ 24-37, Wells Tr. (Ex. 14) at 209:12-24, 215:12-23.

Dr. Wells agrees that ASCOT was not designed to analyze effects in women separately from men; "it was designed [to evaluate] the overall endpoint." Wells Tr. (Ex. 14) at 169:23-170:3. He concedes that the statistical test that was pre-specified in the ASCOT study for identifying differences in efficacy findings between subgroups, including between men and women, is a standard and commonly-used test known as the Cox proportional hazards model. *Id.* at 151:18-21, 152:15-23. [redacted][30]

[30] Dr. Wells notes that the FDA medical reviewer considered the ASCOT heterogeneity test's p-value of 0.08 to be significant based on a conservative approach under which a p-value

[redacted]

Dr. Wells admits that: (1) the ASCOT statistical analysis plan did not call for the use of the Aalen model, Wells Tr. at 152:15-23; (2) neither the ASCOT authors, nor Pfizer, nor FDA used the Aalen model in evaluating the ASCOT data, *id.* at 151:22-152:14; (3) he has never published a peer-reviewed article applying the Aalen model, *id.* at 155:5-9; and (4) he cannot identify any statin study or publication applying the Aalen model to test for differences in efficacy among subgroups of patients, *id.* at 153:4-10. Drs. Abramson and Fleming rely on Dr. Wells's unpublished analysis. *See* Abramson Tr. (Ex. 5) at 30:14-17; Fleming Tr. (Ex. 6) at 212:22-213:14.

4. Dr. G. Alexander Fleming

Dr. Fleming is a physician and former FDA Medical Officer who offers opinions on Pfizer's labeling for Lipitor. Unlike his colleagues with no regulatory experience, he does ***not*** challenge the indication for primary prevention in women. Rather, he seeks to opine that "[t]he ASCOT data did not establish the efficacy of Lipitor in women for primary prevention, and, notwithstanding FDA's agreement with Pfizer's proposed language for the July 2004 label update concerning ASCOT, Pfizer's label was inappropriate and misleading." Fleming Rpt. (Ex. 4) at 6. He would include additional language in the label about the ASCOT data for women. Fleming Tr. (Ex. 6) at 273:2-20.

Dr. Fleming relies "in good part" on Dr. Wells for his opinions regarding ASCOT, but he admits that he did not review or replicate Dr. Wells's methodology or perform any independent analyses himself. *Id.* at 212:22-213:20. Dr. Fleming also relies on Dr. Wells's literature review

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of less than 0.1 (rather than 0.05) was considered significant for evaluating potential safety issues. Wells Rpt. (Ex. 3) at 6 n.4. But this simply further confirms that FDA took this potential difference between efficacy results in men and women into account in deciding to approve Lipitor for primary prevention without regard to gender.

and meta-analysis, but he did not replicate the review and was not aware that over 70% of the patients in Dr. Wells's 2008 meta-analysis were taking pravastatin, rendering that analysis "over representative of pravastatin." *Id.* at 221:19-223:3.

Dr. Fleming concedes that FDA believed when it approved the ASCOT SNDA in 2004 that efficacy had been proven for primary prevention for men and women, that Lipitor was safe for that use, and that the benefits of Lipitor outweighed its risks in both men and women for primary prevention. *Id.* at 223:4-224:10. He also agrees that FDA continues to approve gender-neutral primary prevention labeling for Lipitor and that FDA thus continues to believe that efficacy has been established and that the benefits outweigh the risks for patients using Lipitor as indicated for primary prevention. *Id.* at 224:18-225:14. Dr. Fleming does not opine that Pfizer withheld any relevant data from FDA in connection with ASCOT, and he does not believe that FDA failed to review any relevant data. *Id.* at 224:11-17. He also admits that FDA reviewed more information than he did in reaching its opinion about efficacy for primary prevention. *Id.* 225:21-24. [redacted]

Dr. Fleming also acknowledges that ASCOT was stopped early for benefit and that this can make it challenging to draw conclusions about the small number of events in women. *Id.* at 243:7-245:9. He does not opine that the efficacy of Lipitor for primary prevention for women has not been established, and he concedes that other studies with primary prevention data might fill the gaps that he thinks ASCOT has for women. *Id.* at 227:20-228:23.

II. PLAINTIFFS' EXPERTS' OPINIONS ARE UNRELIABLE AND INADMISSIBLE

Plaintiffs' experts opinions that Lipitor is not effective for primary prevention in women are not scientifically reliable and should be excluded. Pfizer refers to and incorporates herein the standards governing this Court's scrutiny of expert testimony as set forth in Pfizer's concurrently filed Motion to Exclude Plaintiffs' Expert Testimony on General Causation.

A. Plaintiffs' Experts' Opinions Are Not Generally Accepted

Under *Daubert*, "[w]idespread acceptance can be an important factor in ruling particular evidence admissible," and a theory that "'has been able to attract only minimal support within the community' may properly be viewed with skepticism." 509 U.S. at 594 (citation omitted). Courts have thus excluded opinions that "are not generally accepted in the relevant scientific community." *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 569 (W.D. Pa. 2003).

Plaintiffs' experts' opinions that Lipitor is not effective for primary prevention in women are not generally accepted. [redacted] nor any of the national medical associations that have published evidence-based cardiovascular and cholesterol treatment guidelines have ever directed or recommended that Lipitor should not be used for primary prevention in women. To the contrary, as set forth in detail above, FDA and the broader medical and scientific community have concluded that Lipitor and other statins are effective for both men and women for LDL lowering and for primary prevention of CVD, and the evidence has grown over time with increasing study and use of statins in women.

Drs. Abramson, Wells, and Roberts have voiced the view that statins do not work in women for primary prevention for many years in different formats – Dr. Abramson in his 2005 Lipitor litigation and several articles, Dr. Wells in his legal journal in 2008, and Dr. Roberts in her 2012 *Truth About Statins* book and other public statements. Mere publication does not, of course, make a theory generally accepted. *See Am. Honda Motor Co., Inc. v. Allen*, 600 F.3d 813, 817-18 (7th Cir. 2010); *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1165-66 (E.D. Wash. 2009). Their views have never been adopted by public health authorities or the medical community. Rather, "[t]o the extent that [their theory] has been subjected to peer review and publication, it has been rejected by the overwhelming majority of the scientific community." *Whiting v. Boston Edison Co.*, 891 F. Supp. 12, 25 (D. Mass. 1995). It has been confronted repeatedly with studies disproving the claim that only men benefit from statins for primary prevention and with evidence-based treatment guidelines recommending statins based on CVD

risk factors, not gender. It is Plaintiffs' experts' statements that have been controversial, with a lack of agreement on those opinions even among Plaintiffs' experts themselves. Where such controversy exists as to an expert's theory, it "does not indicate … general acceptance." *Lujan v. Cooper Tire & Rubber Co.*, 2008 WL 7489095, at *3 (D.N.M. June 13, 2008).

In addition, as discussed in sections II.B and II.D below, Dr. Wells, Abramson, and Fleming rely heavily on Dr. Wells's novel, unpublished statistical analysis of the ASCOT data, which departs from the generally accepted method for testing for heterogeneity by gender.

B. Plaintiffs' Experts Fail to Address the Totality of the Evidence

"'Scientific' knowledge is generated through the scientific method – subjecting testable hypotheses to the crucible of experiment in an effort to disprove them." *United States v. Bynum*, 3 F.3d 769, 773 (4th Cir. 1993); *accord Black v. Rhone-Poulenc, Inc.*, 19 F. Supp. 2d 592, 598 (S.D. W. Va. 1998). "Epidemiologists use an analytic tool known as the 'null hypothesis,' which postulates that there is no association between a specific exposure and a particular outcome.... The goal of an epidemiological study is to determine whether one can reject the null hypothesis and conclude that, in fact, there is an association between the exposure and the outcome." *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1451-52 (D.V.I. 1994), *aff'd*, 1994 WL 16973481 (3d Cir. Dec. 15, 1994); *accord Chambers v. Exxon Corp.*, 81 F. Supp. 2d 661, 665 (M.D. La. 2000), *aff'd*, 247 F.3d 240 (5th Cir. 2001).

Plaintiffs' experts' theory that Lipitor does not reduce the risk of CVD in women has repeatedly been tested in epidemiological studies, and it has repeatedly failed both in individual trials – such as ASCOT and CARDS, which have shown efficacy with Lipitor for the pre-specified endpoints and no heterogeneity between men and women – and against the totality of the evidence. As set forth above, that evidence includes extensive controlled epidemiological data from dozens of statin trials that included both men and women. The results of those trials have been subjected to numerous, varied meta-analyses by scientists around the world who have looked specifically for differences in effect on CVD risk reduction by gender. Those meta-

analyses, including the CTT's in 2015, which Dr. Abramson agrees represents the "best" evidence to date, Abramson Tr. (Ex. 5) at 606:15-17, have repeatedly found that statins are effective for women for primary prevention.

As a result, Plaintiffs' experts do not and cannot derive their no-efficacy opinions from the totality of the evidence. Instead, they rely on selected studies, selected data points within studies, and their own mostly unpublished criticisms of the peer-reviewed literature to support their conclusions. An expert who "selectively discuss[es] studies most supportive of her conclusions … and fails to account adequately for contrary evidence" should be excluded because "this methodology is not reliable or scientifically sound." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 460-61 (E.D. Pa. 2014). In *Zoloft*, the court rejected a general causation expert's testimony as unreliable where, like Plaintiffs' experts' no-efficacy opinions here, the expert's "conclusions [we]re drawn from trends she observed in a self-selected subset of supportive studies, not the totality of the epidemiological evidence." *Id.* at 461-62. "[A]ny theory that fails to explain information that otherwise would tend to cast doubt on that theory is inherently suspect," and courts have accordingly "excluded expert testimony 'where the expert selectively chose his support from the scientific landscape.'" *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 425 & n.164 (S.D.N.Y. 2005) (citation omitted).

Though more than a decade of additional data and analysis has followed ASCOT and provides extensive further support for Pfizer's and FDA's finding that Lipitor provides primary prevention benefit for women, Plaintiffs' experts rely for their no-efficacy opinions primarily on the ASCOT data. Beyond being methodologically unsound because their opinions fail to account for the totality of evidence, their ASCOT-driven approach is scientifically flawed because it improperly isolates the ASCOT data for women or relies on Dr. Wells's unpublished, non-peer-reviewed, and results-driven heterogeneity test to find no efficacy in women. Plaintiffs' experts admit that ASCOT was not designed or powered to separately test for efficacy in women. It is thus not sound science to base an opinion about efficacy in women solely on the

data collected for women, as Dr. Roberts does. *See* Roberts Rpt. (Ex. 2) at 4-5.[31] This is particularly true when, as Plaintiffs' experts acknowledge, ASCOT ended early for benefit and the number of women and cardiovascular events in women during the trial was small. Instead, as the ASCOT protocol provided, as FDA agreed, and as Dr. Wells recognizes, to determine whether women benefitted from treatment in ASCOT, one should look at whether there is a statistically significant difference in effect by gender by testing for "interaction" or heterogeneity. *See* Wells Tr. (Ex. 14) at 169:17-170:3; Wei Rpt. (Ex. 38) ¶¶ 55-59. [redacted]

Drs. Wells and Fleming also rely on Dr. Wells's limited, self-described "meta-analysis" that he published in 2008 in a law journal (on which he served as editor) to help support an argument about preemption by the lead author, a lawyer.[32] *Id.* ¶¶ 16-23; Wells Tr. (Ex. 14) at 195:2-196:15, 197:4-9. Dr. Wells's analysis included only five studies, did not reflect the totality of the Lipitor or statin primary prevention data even as of 2008 (it excluded CARDS, for example), and looked almost exclusively at studies that involved pravastatin, not Lipitor. Wells Tr. (Ex. 14) at 76:1-77:24, 190:1-5, 197:19-199:15. It was not peer-reviewed and did not account for the totality of evidence then. Its unreliability has only grown since then.

Plaintiffs' experts also fail either to account for, or to apply any sound methodology refuting, the findings of the numerous studies, meta-analyses, and treatment guidelines cited

[31] Dr. Roberts makes the same error with respect to CARDS. Her statement that "there was no evidence that treatment with atorvastatin lowered cardiac risk" in women in CARDS, Roberts Rpt. (Ex. 2) at 7, is inaccurate and unsound. It is based solely on the data from women, which were not intended to provide a basis for drawing a conclusion about efficacy in women.

[32] *See* Eisenberg & Wells, *Statins and Adverse Cardiovascular Events in Moderate-Risk Females: A Statistical and Legal Analysis with Implications for FDA Preemption Claims*, 5 J. of Empirical Legal Studies 507 (2008) (Ex. 51).

above that statins provide primary prevention benefit without regard to gender. Dr. Wells, for example, admitted that he had not reviewed the 2013 AHA and ACC cholesterol treatment guidelines endorsing statins for primary prevention in women, and he did not know what studies and data they relied upon. *See* Wells Tr. (Ex. 14) at 117:6-16, 126:9-130:1. He testified: "I haven't analyzed the data. … They are an expert panel, so I don't have any reason to not believe [their findings]. But … I don't have the data, and I'm being asked to evaluate something when I haven't looked at the data." *Id.* at 125:13-22. He conceded that the statin studies and data those medical associations relied on were clearly set forth in the publication. *See id.* at 126:9-22. Dr. Fleming also concedes that he did not review all potentially relevant clinical trials for Lipitor, including studies that provided additional information about use for primary prevention, and did not analyze any data. Fleming Tr. (Ex. 6) at 227:20-229:9, 317:15-17.

Drs. Abramson, Wells, and Roberts each discount the results and findings of some of the most powerful sources of evidence of efficacy for primary prevention in women, but they do so through criticisms and manipulation of the data that they cannot reconcile with the studies and that are not generally accepted. Dr. Abramson, for example, claims that the CTT (2015) and Cochrane (2013) meta-analyses do not provide evidence that statins offer primary prevention benefit to women because, he asserts, they looked at the effects of Lipitor "on major vascular events," not just death, heart attack, or stroke. Abramson Rpt. (Ex. 1) ¶¶ 247-248. He claims that reducing the risk of revascularizations, such as angioplasty or bypass, should not be considered a beneficial cardiovascular outcome for purposes of evaluating the efficacy of Lipitor and other statins. *Id.* ¶¶ 248, 252. Yet he admits that Lipitor is properly approved to reduce the risk of revascularization in patients without CHD, Abramson Tr. (Ex. 5) at 384:4-6, 394:11-19; revascularization involves major heart surgery or a complex medical procedure, *id.* at 386:1-387:5; and reducing the risk of revascularization with statins is "a good thing," *id.* at 395:9-15.

To support his sweeping view that the major statin meta-analyses "do not provide evidence that cholesterol-lowering statin drugs provide benefit to primary prevention women" because they include "major vascular events" as part of a "composite endpoint," Abramson Rpt.

(Ex. 1) ¶ 259, Dr. Abramson relies on generic assertions about the limitations of clinical trial data and his view that revascularization is not "as dependable" an outcome "as hard outcomes." Abramson Tr. (Ex. 5) at 395:9-396:8. His bare criticisms of the generally accepted methods for evaluating statin efficacy data using pooled randomized clinical trial data and multiple endpoints – which scientists and public health authorities have done for the last two decades – do not withstand scrutiny. *See* Sacks Rebuttal Rpt. (Ex. 36) at 6-10. They serve his personal advocacy agenda but lack the objectivity required of an expert seeking to proffer scientific testimony to a jury.

Similarly, Dr. Wells broadly asserts that the conclusions of recent meta-analyses finding efficacy for women for primary prevention "are flawed," Wells Rpt. (Ex. 3) ¶ 25, because, he says, they "ignor[e] the primary/secondary prevention distinction or … combin[e] JUPITER with other studies." *Id.* ¶ 37; *see also id.* ¶¶ 26-36; Wells Tr. (Ex. 14) at 228:6-24. But Dr. Wells has not published these opinions or critiques in any peer-reviewed journal, and he concedes that every meta-analysis of statin efficacy data published since JUPITER has included JUPITER. Wells Tr. (Ex. 14) at 229:9-21. He admits that he does not have the data on which the CTT authors relied for their 2015 meta-analysis, has never done any meta-analysis of his own of that data, and cannot disagree with the CTT authors' conclusions. *Id.* at 209:6-210:20. Dr. Roberts makes a similar claim as to why she, unlike FDA and the authors of the meta-analyses and guidelines cited above, does not believe the efficacy data from JUPITER provide evidence of primary prevention benefit in women. Roberts Rpt. (Ex. 2) at 6. But she has not independently analyzed the JUPITER data or published any peer-reviewed article or analysis about it. Roberts Tr. (Ex. 12) at 315:25-316:8. Nor was she familiar with published responses by the JUPITER study authors to criticisms she voiced in her *Truth About Statins* book based on articles by Dr. Abramson and others. *Id.* at 305:14-306:4, 307:23-313:5.

Dr. Wells also disregards secondary prevention studies and even primary prevention studies, such as CARDS, that he does not believe should be considered primary prevention studies. Wells Tr. (Ex. 14) at 88:1-91:9, 114:5-115:7. He does so even though he agrees they

show efficacy in women and he cannot identify any biological reason why Lipitor would work for women to prevent a second heart attack but not a first. Plaintiffs' experts' "selectivity in defining the universe of relevant evidence" renders their efficacy opinions unreliable and inadmissible. *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004).

C. Plaintiffs' Experts Have No Biologically Plausible Explanation

Beyond conflicting directly with the scientific community's findings based on the totality of data, Plaintiffs' experts' hypothesis that Lipitor works for primary prevention only in men and not in women lacks any biological foundation. An expert's "inability to show a mechanism," or offer "a testable biologic explanation," for an opinion about how a substance causes an effect in the body, "which is important to the Court's review of scientific reliability, demonstrates a faulty methodology that is not scientifically valid." *Soldo*, 244 F. Supp. 2d at 571-72. Just as plaintiffs claiming a medicine causes an adverse effect need experts who can reliably identify a biologically plausible mechanism of causation, Plaintiffs here need experts who can offer a "testable biological explanation" for why Lipitor would reduce the risk of CVD in men but not in women with the same level of risk. Without a reliable biological foundation, "plaintiffs' expert opinions amount to speculation and potentialities," are "built on an unsupported hypothesis, and [are] thus fundamentally flawed and must be excluded." *In re Bausch & Lomb, Inc. Contact Lens Solution Prods. Liab. Litig.*, 2009 WL 2750462, at *10 (D.S.C. 2009).

Plaintiffs' experts have not identified any biological reason why women would not benefit from statin therapy in the same manner as men with equivalent CVD risk. For example, Dr. Wells does not "know any reason why elevated LDL cholesterol would lead to atherosclerosis in men, but not in women." Wells Tr. (Ex. 14) at 54:14-18; *see also* Gale Tr. (Ex. 10) at 317:20-318:22. Neither he nor Drs. Roberts or Abramson can explain how Lipitor can be equally effective in lowering LDL in men and women but not provide primary prevention benefit in both. Dr. Wells agrees the data show statins are effective in secondary prevention of heart attacks and strokes in women, *id.* at 89:14-18; 95:21-96:2, yet neither he nor Dr. Roberts

can identify "any biologic difference between men and women that would explain why men would receive a cardiovascular benefit for the first heart attack or stroke, and women would only receive benefit for the second heart attack or stroke." *Id.* at 111:7-19; Roberts Tr. (Ex. 12) at 166:21-167:3. Dr. Abramson was also unable to identify any biological explanation for why Lipitor would work for primary prevention for men but not women with equivalent CVD risk. Abramson Tr. (Ex. 5) at 56:22-57:14. Nor does Dr. Fleming offer any biological foundation for his view that that the ASCOT data do not support a primary prevention indication for women. Rather, he admits "the [ASCOT] data were very compelling for men and ***there's good reason to believe that women would not differ substantially from men just from the biology involved***." Fleming Tr. (Ex. 6) at 271:10-272:3 (emphasis added).

D. Plaintiffs' Experts Rely on Flawed, Results-Driven Re-Analyses of the Data

"Coming to a firm conclusion first and then doing research to support it is the antithesis of" the scientific method. *Claar v. Burlington N. R.R. Co.*, 29 F.3d 499, 502-03 (9th Cir. 1994). It is an "internally inconsistent" methodology, *Phillips v. Am. Honda Motor Co.*, 238 F. App'x 537, 541 (11th Cir. 2007), that "has been contrived to reach a particular result." *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1293 n.7 (11th Cir. 2005). Here, Drs. Wells, Abramson, and Fleming rely on Dr. Wells's novel, unpublished heterogeneity testing of the ASCOT data, which he developed for his litigation report and is inconsistent with the published ASCOT data and the analyses Pfizer and FDA did that followed the pre-specified statistical plan for ASCOT.

The Supreme Court addressed similar issues in *Daubert*. There, the plaintiffs' experts opined that a drug caused birth defects based, in part, upon "the 'reanalysis' of previously published epidemiological (human statistical) studies"—reanalyses that were, like Dr. Wells's ASCOT reanalysis, "'unpublished, not subjected to the normal peer review process and generated solely for use in litigation.'" 509 U.S. at 583-85. On remand, the Ninth Circuit noted that "[o]ne very significant fact to be considered is whether the experts … developed their opinions expressly for purposes of testifying," such that the only "review" their work received

would be in the courtroom. *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995). Dr. Wells's non-standard and non-peer-reviewed ASCOT heterogeneity testing, on which Drs. Abramson and Fleming also rely, is solely a litigation-driven, *post hoc* analysis designed to manipulate the data in a manner that ostensibly supports his preordained opinion. It is "driven by h[is] desire to confirm h[is] *a priori* hypothesis" – that Lipitor does not have primary prevention benefit for women. *Zoloft*, 26 F. Supp. 3d at 457 n.25.

In addition, to the extent that Drs. Abramson and Roberts previously advocated against the use of statins for primary prevention in women and have criticized pharmaceutical companies and FDA in writings and other public statements, they asserted those views based on personal opinions and criticisms of published studies, not any original analysis of information relating to Lipitor and efficacy in women.[33] Dr. Abramson has long-contended, for example, that the authoritative cholesterol treatment guidelines are promulgated by expert panels tainted by pro-industry bias. *See, e.g.*, Abramson Rpt. (Ex. 1) ¶ 232; Abramson Tr. (Ex. 5) at 248:5-25. Dr. Roberts asserts similar views in her book. *See supra* Part I.D.2. Neither supports these accusations with any fact, and Dr. Abramson admits that he has no evidence that any company improperly influenced the guidelines. *See* Abramson Tr. (Ex. 5) at 404:8-405:25. Dr. Abramson even admits that he applies different standards to his litigation work and has offered opinions in litigation, including his opinions here, that he was not comfortable endorsing in a professional setting, including in his role advising Wells Fargo about ways to reduce unnecessary spending on medicines. *See supra* Part I.D.1.

Courts have excluded experts who have "become[] … advocate[s] for a cause," because they "depart[] from the ranks of … objective expert witness[es], and any resulting testimony would be unfairly prejudicial and misleading." *Viterbo v. Dow Chem. Co.*, 646 F. Supp. 1420,

[33] Dr. Abramson was a plaintiffs' expert in prior Lipitor litigation when he co-authored a comment in 2007 that described in general terms a pooled analysis of statin data claiming it showed no efficacy for primary prevention in women. Abramson et al., *Are lipid-lowering guidelines evidence-based?*, 369 Lancet 168 (2007) (Ex. 52). The analysis was not published.

1425 (E.D. Tex. 1986), *aff'd*, 826 F.2d 420 (5th Cir. 1987); *see also In re Air Crash Disaster at Detroit Metro. Airport on Aug. 16, 1987*, 737 F. Supp. 427, 430 (E.D. Mich. 1989), *aff'd sub nom. Rademacher v. McDonnell Douglas Corp.*, 917 F.2d 24 (6th Cir. 1990). Their opinions do not meet Rule 702's "core requirement … that expert testimony rest on 'knowledge,' a term that 'connotes more than subjective belief or speculation.'" *Rezulin*, 309 F. Supp. 2d at 543 (quoting *Daubert*, 509 U.S. at 590).

E. Plaintiffs' Experts' Opinions Are Misleading and a Threat to Public Health

"'[E]xpert evidence can be both powerful and quite misleading.'" *Daubert*, 509 U.S. at 595 (citation omitted). For this reason, scientific journals employ peer-review processes and conflict-of-interest disclosure requirements before publishing studies and articles, and courts apply heightened and multi-faceted scrutiny to scientific evidence proffered as expert testimony. Plaintiffs should not be permitted to misinform lay jurors and the public about the state of the science on the risks and benefits of Lipitor through experts whose views are not simply in the minority but have been unequivocally rejected by mainstream science and medicine.

A recent study in the *Medical Journal of Australia* highlights the consequences of such misinformation. The study found a "significant and sustained" reduction in statin use after the Australian Broadcasting Corporation aired a two-part series questioning the link between high cholesterol and CVD and the benefits of statins.[34] Based on pharmacy data, the authors estimated that more than 28,000 patients stopped using statins after the series and predicted that the changes in statin use "could result in between 1,522 and 2,900 preventable, and potentially fatal, major vascular events."[35] The series has been withdrawn in the face of "[c]onsiderable backlash from the medical community[,] including criticism for misleading patients."[36]

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[34] Schaffer et al., *The Crux of the Matter: Did the ABC's* Catalyst *Program Change Statin Use in Australia?*, 202 Med. J. Austl. 591, 591, 593 (2015) (Ex. 53).

[35] *Id.*

[36] *Id.* at 591. A similar response followed when Drs. Abramson and Nicholas Jewell, another statistician serving as an expert for Plaintiffs here, published an article in the British Medical Journal (BMJ) in 2013 (after Dr. Abramson had been retained by Plaintiffs' counsel

III. PLAINTIFFS' EFFICACY CLAIMS ARE PREEMPTED BY FEDERAL LAW

Even if Plaintiffs' experts' efficacy opinions survived *Daubert* – and they should not – they should be excluded for the independent reason that Plaintiffs cannot maintain such claims because they are preempted by federal law. A state law requirement that conflicts with federal law is preempted under the Supremacy Clause of the U.S. Constitution. *See* U.S. Const. art. VI, cl. 2. "Federal law impliedly preempts state law 'where it is impossible for a private party to comply with both state and federal requirements.'" *Celexa*, 779 F.3d at 40 (quoting *Bartlett*, 133 S.Ct. at 2476-77) (internal quotation marks and citation omitted). Here, it would be impossible for Pfizer to comply with any claimed state law duty to change the Lipitor label with respect to its primary prevention indication or otherwise tell doctors and patients that Lipitor is not effective for primary prevention in women without violating Pfizer's obligations under federal law and frustrating Congress's objectives in delegating authority over prescription drug labeling to FDA. Indeed, the Supreme Court has made clear that state-law claims that seek to impose a duty to alter drug labeling in a way that conflicts with federal law are preempted. *See Bartlett*, 133 S. Ct. at 2476-80; *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2574-76, 2580-81 (2011).

Plaintiffs' claims threaten to precipitate a public health crisis by advancing misinformation about statins. The FDA is statutorily charged by Congress with "promot[ing] the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products." 21 U.S.C. § 393(b)(1); *see id.* § 352(n). The FDA must "protect the public health by ensuring that … human … drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B). To this end, "the FDA employs a comprehensive scheme

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here) that argued that "the evidence does not show that the benefits of statins in low risk patients outweigh the harms." Abramson et al., *Should people at low risk of cardiovascular disease take a statin?*, 347 BMJ f6123 (2013) (Ex. 54). Dr. Abramson and his coauthors relied on an erroneous characterization of an observational study about side effects from statin use. The BMJ required a correction and the journal's editor published an editorial describing the errors in the article and explaining that the editorial was intended "to alert readers, the media, and the public to the withdrawal of these [incorrect] statements so that patients who could benefit from statins are not wrongly deterred from starting or continuing treatment because of exaggerated concerns over side effects." Godlee, *Adverse effects of statins*, 348 BMJ 11 (2014) (Ex. 55).

of premarket screening and post-market surveillance to ensure the safety and efficacy of all licensed medications." *Grundberg*, 813 P.2d at 96. A lay jury should not be asked to second-guess the informed medical and scientific judgment committed by Congress to FDA in the interest of promoting and protecting the public health.

In *Prohias*, in which Dr. Abramson was also an expert for plaintiffs claiming Lipitor is not effective for primary prevention in women, the court dismissed as preempted all such claims relating to any marketing of Lipitor after FDA approved Lipitor for primary prevention in 2004. *Prohias*, 490 F. Supp. at 1234-35. Pfizer's advertisements "derive[d] from" the label and "[f]or this reason, the plaintiffs' efforts to hold Pfizer liable for the advertisements conflict[] with the FDA's jurisdiction over drug labeling, and specifically its approval of Lipitor to reduce the risk of heart disease in some patients. Those claims are therefore preempted by federal law." *Id.* at 1234. In addition, the "advertisements were not misleading as a matter of law. The information included in the labeling of a drug reflects a determination by FDA that the information is not 'false or misleading.' 21 C.F.R. § 314.125(b)(6)." *Id.* at 1235.[37] The same analysis applies here and is consistent with the post-*Prohias* Supreme Court decisions cited herein.

The First Circuit's recent decision in *Celexa* is also instructive because it also involved allegations that a medication was not effective for an FDA-approved use. Plaintiffs paid for Lexapro, an antidepressant, that was prescribed for their adolescent son. Plaintiffs alleged that the clinical trial data on which the manufacturer relied to obtain FDA approval for Lexapro for adolescents did not establish that the medicine was more effective for that use than placebo. They brought claims under California's consumer protection laws and sought to represent a class of California consumers who purchased Lexapro for adolescent use. *Celexa*, 779 F.3d at 37-38. Plaintiffs disagreed with the manufacturer's and FDA's analysis of the study data submitted with

[37] After the court subsequently granted summary judgment dismissing Plaintiffs' claims as to pre-2004 written advertising, the *Prohias* plaintiffs voluntarily dismissed with prejudice their remaining claims, relating to pre-2004 non-written promotional activities. *Prohias v. Pfizer, Inc.*, No. 1:05-cv-22658, Order on Motion for Summary Judgment [Dkt. 88] (S.D. Fla. Aug. 16, 2007); Final Order of Dismissal With Prejudice [Dkt. 99] (S.D. Fla. Jan. 9, 2008).

the supplemental NDA for adolescent use, and they claimed that the manufacturer had not submitted adequate evidence of efficacy for treating adolescent depression. *Id.* at 38. They claimed that, as a result, the approved label was "'misleading and inadequate.'" *Id.*

The First Circuit affirmed the district court's order dismissing the complaint. It did so on the ground that plaintiffs' claims were preempted by federal law. *Id.* at 43. The court observed that plaintiffs were seeking "to impose liability on [defendant] Forest because of what Lexapro's FDA-approved label state[d] or fail[ed] to state. In other words, ... Forest would need to change Lexapro's label in order to avoid liability under state law." *Id.* at 40. The court held that under the Supreme Court's decisions in *Wyeth v. Levine*, 555 U.S. 555 (2009), and *Mensing*, 131 S.Ct. 2567, which addressed whether and when a plaintiff may maintain state-law claims based on allegations that a prescription drug label is inadequate or inaccurate, the *Celexa* plaintiffs could maintain their claims only if the manufacturer could have made a change to the Lexapro label under what is known as the Changes Being Effected (CBE) regulation, 21 C.F.R. 314.70(c)(6)(iii). *Id.* at 41. That regulation allows a manufacturer to make limited label changes without first seeking FDA approval under certain circumstances, all of which require that the change "reflect newly acquired information." 21 C.F.R. 314.70(c)(6)(iii).

The First Circuit held that the manufacturer could not have made the change to the Lexapro label that plaintiffs there alleged should have been made because plaintiffs were not relying on any "newly acquired information." As the court explained, "CBE changes rest on the existence of 'newly acquired information.' 21 C.F.R. 314.70(c)(6)(iii). A state law duty to initiate such a change is therefore not by its nature a second guess of an FDA judgment." *Celexa*, 779 F.3d at 41 (citing *Levine*, 555 U.S. at 578-79). In other words, Congress has made "the FDA … the exclusive judge of safety and efficacy based on information available at the commencement of marketing" a new medicine or new indication for an approved medication. *Id.* Here, as in *Celexa*, Plaintiffs do not base their claim that the primary prevention indication in the Lipitor label is inaccurate or misleading on any "newly acquired information." Instead, Plaintiffs and their experts rely on information "that was plainly known to the FDA prior to

approving" the primary prevention indication for Lipitor in 2004. *Id.* at 43. *See, e.g.*, Wells Tr. (Ex. 14) at 132:21-133:12; Abramson Tr. (Ex. 5) at 21:13-23, 25:25-27:1, 32:2-33:5, 358:22-359:1. Indeed, Dr. Fleming admits that he is not offering an opinion that Pfizer wrongly failed to submit a CBE. Fleming Tr. (Ex. 6) at 90:16-91:6.

For purposes of a CBE label change, "newly acquired information" does not include clinical data already submitted for FDA review. 21 C.F.R. 314.3(b). In addition, under the CBE regulation, "new analyses of previously submitted data (e.g., meta-analyses)" do not satisfy the requirement of "newly acquired information" unless they consist of "studies, events or analyses [that] reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. 314.3(b).[38] Plaintiffs have not identified or relied on any such studies or analyses here. To the extent their experts rely on Dr. Wells's novel analysis of previously submitted ASCOT data and meta-analysis of data from various statin trials, the analyses involve data relating to efficacy rather than risk and do not meet the definition of "newly acquired information." Requiring a manufacturer "to add information to the labeling … based solely on data previously submitted to the FDA," as Plaintiffs seek to do here, "would undermine FDA's approval process and could result in unnecessary or confusing information being placed in the labeling for a drug." Supp'l Applications Proposing Labeling Changes for Approved Drugs, Biologics, & Med. Devices, 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008).

Nor can Plaintiffs rely on their experts' criticisms of Pfizer's and FDA's analysis of the ASCOT data. In *Celexa*, the First Circuit expressly rejected plaintiffs' attempt to rely on what they claimed was an inappropriate statistical analysis of study data that the Lexapro manufacturer provided to FDA as part of its supplemental NDA for adolescent use. *Celexa*, 779 F.3d at 42-43. The court explained: "This [alleged inappropriate inclusion of certain patients in the study data analysis] is the basis of plaintiffs' allegation that [the study] was 'manipulated.'

[38] A manufacturer may "delete false, misleading, or unsupported indications for use or claims for effectiveness" based on new information, 314.70(c)(6)(iii)(D), but it may not otherwise add to or modify labeling statements relating to efficacy. 314.70(c)(6)(iii)(A)-(C).

Plaintiffs make no claim, however, that this information was unknown to the FDA prior to label approval." *Id.* at 43. Similarly, here, Plaintiffs assert that their expert's novel and litigation-driven statistical analysis of the ASCOT data requires a Lipitor label that limits the primary prevention approval to men. But like plaintiffs in *Celexa*, who admitted FDA knew about the efficacy data when it decided to approve the indication for adolescent use, *id.*, Plaintiffs do not and cannot dispute that FDA had the same ASCOT data on which Dr. Wells and Plaintiffs' other experts rely for their analysis. Nor do they or can they dispute that FDA was aware of the limitations and inconclusive nature of the ASCOT data for women alone.

Here, as in *Celexa*, Plaintiffs' "no efficacy" claims and expert opinions conflict directly with FDA's labeling decision based on its own expert review of the data at issue. Here, as there, Pfizer "could not independently change its label to read as plaintiffs say it should." *Id.* at 43. Plaintiffs' efficacy claims are preempted by federal law. Specifically, Plaintiffs should be precluded from making any claim that: (1) Lipitor should not have been indicated for primary prevention in women; or (2) the label should have stated that Lipitor is ineffective in women.

CONCLUSION

For the foregoing reasons, Pfizer respectfully requests that this Court grant its motion and exclude Plaintiffs' experts' testimony and other evidence, claims, or statements that Lipitor is not effective for reducing the risk of heart disease in women who have multiple risk factors for heart disease but who have not been diagnosed with heart disease.

DATED: July 24, 2015

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CERTIFICATE OF SERVICE

I hereby certify that, this 24th day of July 2015, I have electronically filed a copy of the above and foregoing with the Clerk of the Court using the ECF system, which sent notification of such filing to counsel of record.

/s/ Mark S. Cheffo
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